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## Abstract

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**KEYWORDS:** renal transplantation,  $\gamma$ -GTP, intrahepatic cholestasis, liver injury, azathioprine

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## **NONICTERIC LIVER DAMAGE WITH A GAMMA-GLUTAMYL TRANSPEPTIDASE LEVEL OF 5,609 UNITS/L IN A RENAL-TRANSPLANT RECIPIENT RECEIVING AZATHIOPRINE**

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**Abstract.** A 26-year-old male with renal allograft, who received immunosuppressive treatment with azathioprine, presented marked elevations of serum biliary tract enzymes, such as gamma-glutamyl transpeptidase (5,609 units/l) and alkaline phosphatase (60.5 Bessey-Lowry units), 14 months after transplantation. Two months later the patient became icteric; he died of respiratory failure 19 months after the renal allograft. Postmortem examination revealed intrahepatic cholestasis with minimal inflammatory cell infiltration, indicating drug hepatotoxicity.

**Key words :** renal transplantation,  $\gamma$ -GTP, intrahepatic cholestasis, liver injury, azathioprine.

Hepatic dysfunction occurs in renal allograft recipients (1, 2). Hepatitis B virus and cytomegalovirus infections and immunosuppressive drugs, such as azathioprine, have been considered to cause the dysfunction (2, 3). However, there are few reports concerning elevated serum biliary tract enzyme activities during the post-transplant period. Herein, we report a renal allograft recipient who remained nonicteric despite extensive liver injury. Peak serum levels were as follows: serum gamma-glutamyl transpeptidase ( $\gamma$ -GTP), 5,609 units/l (160-fold increase over normal levels); alkaline phosphatase (Al-Pase), 60.5 Bessey-Lowry units (21-fold increase), and leucine aminopeptidase (LAP), 2,286 units (35-fold increase).

### **CASE REPORT**

A 26-year-old male was admitted to the First Department of Surgery, Okayama University Hospital, because of jaundice and fever on February 23, 1979. The patient had been undergoing hemodialysis for renal failure since 1972. During this period, he had received blood transfusions totalling 6,000 ml, most recently on August 3, 1977. He underwent renal transplantation on August 4, 1977. His 58-year-old mother was the donor. On the day of surgery immunosuppressive treatment with 200 mg azathioprine and 60 mg prednisolone daily was initiated; thereafter, the doses were tapered to maintenance levels. The patient experienced con-

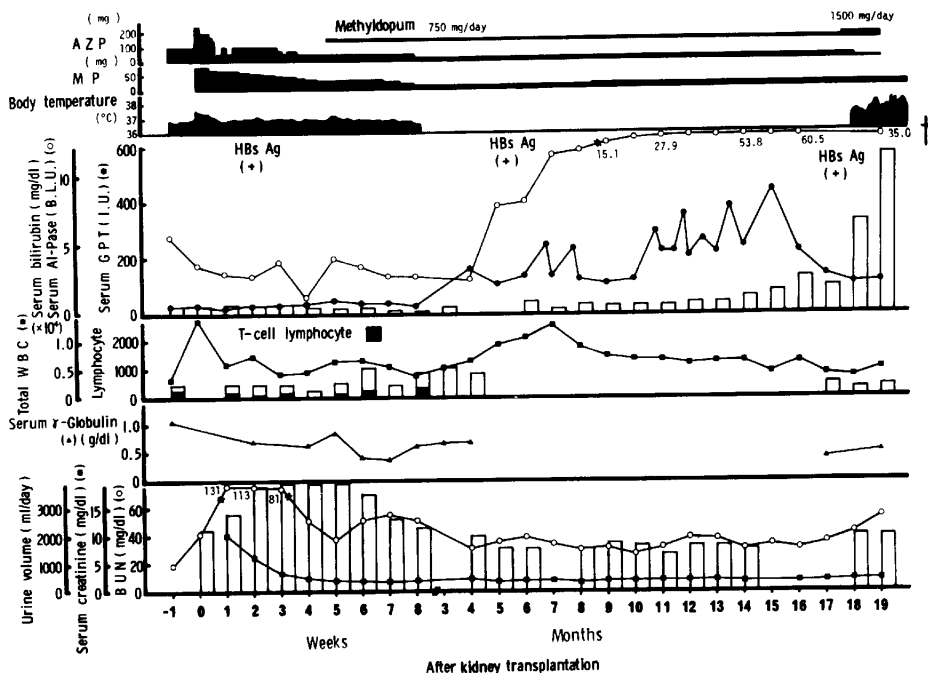


Fig. 1. Clinical course, laboratory data and therapeutic procedures. AZP: azathioprine; MP: methylprednisolone.

tinued hypertension, and a bilateral nephrectomy was performed in September 1977. Methyldopum administration was started, 750 mg per day, following the nephrectomy (Fig. 1).

In January 1978, serum  $\gamma$ -GTP, Al-Pase and LAP activities began to increase, reaching peak values during October 1978 of 5,609 units/l (normal 3-35) serum  $\gamma$ -GTP, 60.5 Bessey-Lowry units (normal 0.8-2.9) Al-Pase and 2,000 units (normal 20-65) LAP. However, the patient did not exhibit jaundice. In the middle of November 1978, serum bilirubin levels increased, and the patient was admitted to a local hospital. Because of associated high fever, the patient was transferred to Okayama University Hospital.

Physical examination upon admission revealed a chronically ill, jaundiced and anemic man. Numerous scratch marks were present. Heart and lung examinations were normal. Pretibial pitting edema was present. Blood pressure was 176/130 mmHg. The hemoglobin was 9.5 g per 100 ml; hematocrit 27 %; red blood cell count  $280 \times 10^4$  per  $\text{mm}^3$ ; white blood cell count  $3,700$  per  $\text{mm}^3$  (band form of neutrophils 8 %, segmented neutrophils 70 %, monocytes 8 %, and lymphocytes 14 %), and platelet count  $18.2 \times 10^4$  per  $\text{mm}^3$ . The total serum bilirubin was 8.2 mg per 100 ml (direct of 6.0; indirect 2.2); Al-Pase 36.0 BLU; serum

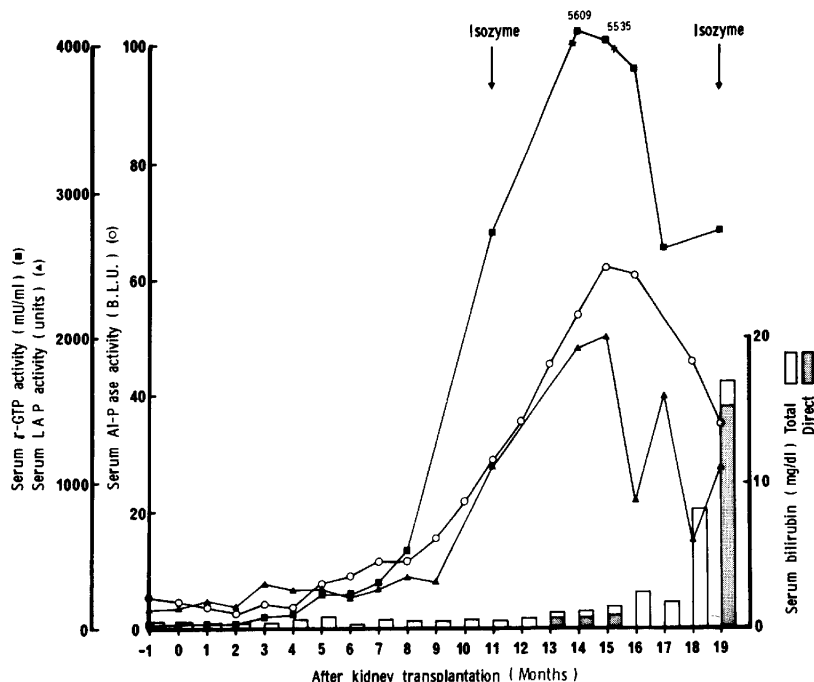


Fig. 2. Serum biliary tract enzyme activities following renal transplantation.

glutamic oxaloacetic transaminase (GOT) 157 IU (normal 11-40); serum glutamic pyruvic transaminase (GPT) 116 IU (normal 6-35); lactic acid dehydrogenase (LDH) 766 Wroblewski units (normal 100-600); LAP 2,286 units, and  $\gamma$ -GTP 3,150 units/l. Serum total cholesterol was 780 mg per 100 ml and total protein 5.8 g per 100 ml (albumin 3.7 g,  $\gamma$ -globulin 0.5); blood urea nitrogen 31 mg per 100 ml, and creatinine 1.8 mg per 100 ml. The hepatitis B surface antigen (HBsAg) was present, but antibody to HBsAg (anti-HBsAg) was lacking. Antibodies to cytomegalovirus, herpes simplex virus type I, and adenovirus were all absent.

Abnormal biochemical and serological parameters are depicted in Fig. 2. Isozyme patterns of serum Al-Pase,  $\gamma$ -GTP, and LAP were determined on cellulose acetate membranes (Fig. 3). The isozyme patterns of  $\gamma$ -GTP, when the patient was non-icteric in the 11th and icteric in the 19th month after transplantation, presented marked elevation of the  $\beta$ -globulin fraction; this was particularly true in the icteric stage. LAP isozymes were increased similarly in the  $\alpha_2$  to  $\beta$  fraction. The Al-Pase isozyme pattern in the 19th month, when jaundice was marked, revealed increases in isozymes I and II. These patterns were attributed to intrahepatic cholestasis, which became severe in the terminal stage.

Azathioprine (AZP) administration induced an immunosuppressed state from approximately 7 weeks following transplantation as indicated by low  $\gamma$ -globulin

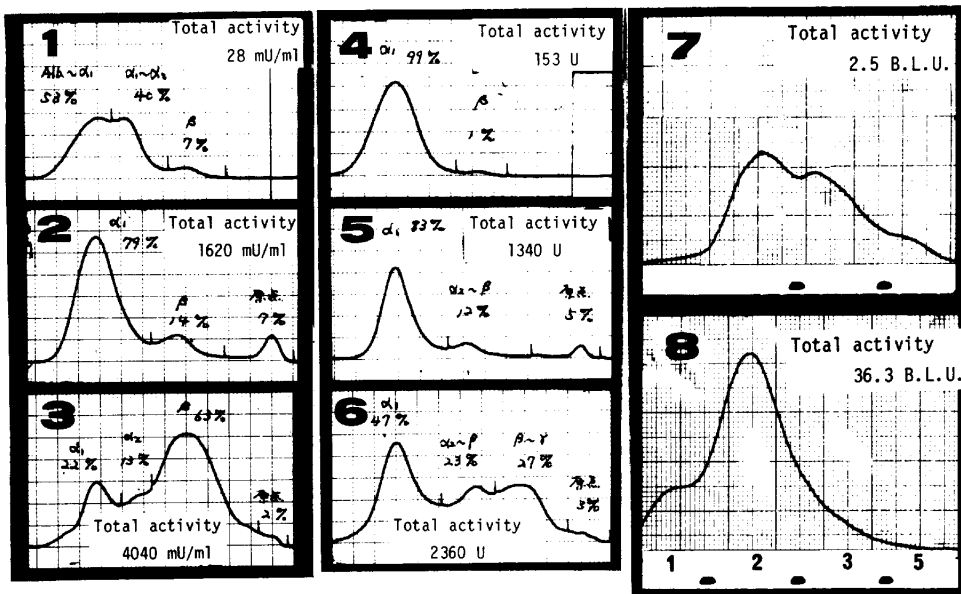


Fig. 3. Isozyme patterns of  $\gamma$ -GTP (1, 2 and 3), LAP (4, 5 and 6) and ALPase (7 and 8) on cellulose acetate electrophoresis. The isozyme pattern of a healthy 32-year-old man (1, 4 and 7). The isozyme patterns of the patient on July 24, 1978 (2 and 5), and on March 7, 1979 (3, 6 and 8).

and T-cell levels (Fig. 1). After doses of azathioprine and methylprednisolone (MP) were diminished to 25 mg and 16 mg daily, respectively, during the 8th week, peripheral white blood cell counts increased slowly. Serum GPT activity rose to 200 IU, and serum biliary tract enzyme activities also increased. Serum cholesterol concentrations were elevated markedly. Azathioprine was discontinued on February 17, 1979 (18 months after the operation), but prednisolone, 20 mg daily, was continued. High fever continued despite various antibiotic regimens, and dyspnea appeared on March 5, 1979. Renal function was severely impaired and hemodialysis reinitiated on March 6, 1979. However, jaundice and dyspnea increased rapidly, and the patient died of acute respiratory failure on March 13, 1979.

Postmortem examination of the liver and kidney allograft was performed. The liver was normal in shape and consistency. The surface was dark and greenish-brown. Periportal fatty degeneration and centrilobular liver cell degeneration were observed (Fig. 4). However, even in the most extensively degenerated zones there was little inflammatory cell infiltration. Biliary thrombi and proliferation of bile ductules also were observed. However, there was no dilatation or obstruction of the extrahepatic bile ducts. These lesions were consistent with drug-induced

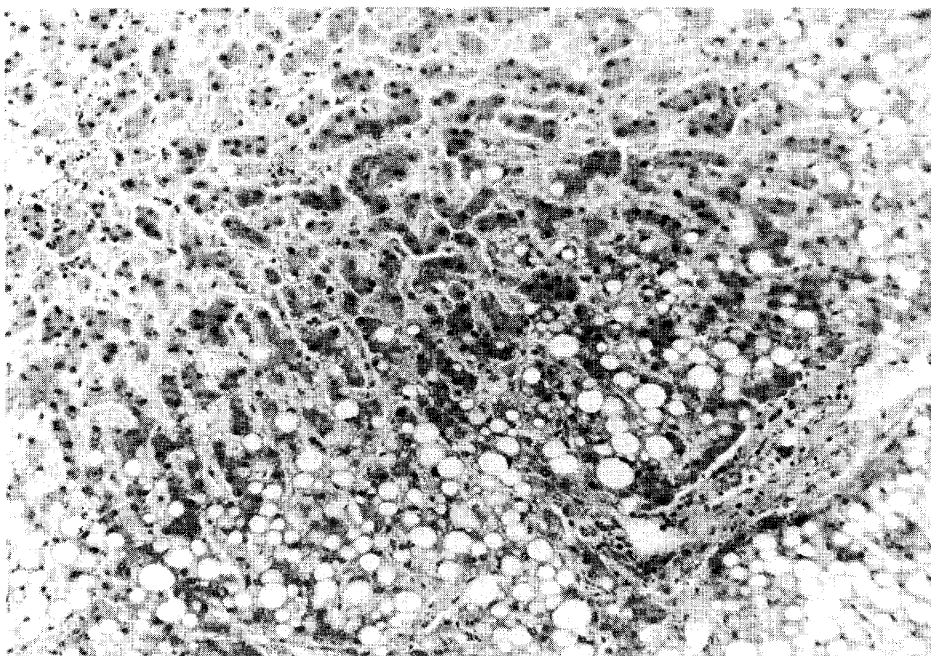


Fig. 4. Microscopic findings of the liver. Hematoxylin-eosin,  $\times 250$ .

liver disease. The kidney allograft weighed 225 g and histologically demonstrated chronic rejection.

#### DISCUSSION

A rise in serum  $\gamma$ -GTP is usually assumed to be due to either hepatobiliary disease or hepatic microsomal enzyme induction (4). In uremic patients, serum  $\gamma$ -GTP activity remains normal (5). Elevated activity following renal transplantation suggests concurrent hepatobiliary disease, or drug-related hepatic microsomal enzyme induction (5). In a series of 71 transplant recipients, 5 of which had received microsomal enzyme-inducing drugs, the incidence of elevated  $\gamma$ -GTP activity (slight elevation of 35-250 units/l) was 28 %, being significantly higher than in nondialysed and dialysed uremic patients (5). In 67-85 % of epileptic patients treated with various anticonvulsant drugs, serum  $\gamma$ -GTP activity was elevated (35-220 units/l) (6).

To our knowledge, the serum  $\gamma$ -GTP activity in the present patient is the highest reported in a renal transplant recipient. The  $\gamma$ -GTP levels correlated well with elevated levels of LAP and Al-Pase. The isozyme patterns of the three biliary tract enzymes suggested the presence of intrahepatic cholestasis, and postmortem examination of the liver indeed revealed such drug-induced liver injury. Takahashi *et al.* (7) also reported 3 patients with high  $\gamma$ -GTP activity after renal transplanta-

tion (1,608, 1,764 and 1,300 units/l). These patients developed jaundice 14, 7 and 5 months after the operation. The isozyme patterns were consistent with intrahepatic cholestasis.

Azathioprine is known to produce a dose-related cholestasis syndrome in dog (8) and man (9). Patients with chronic liver diseases are more susceptible to azathioprine-induced cholestasis than those with normal livers (10). Severe intrahepatic cholestasis following renal transplantation with adjunct azathioprine therapy has been reported previously (11, 12). The issue has been obscured, in most instances, by failure to exclude other causes of hepatic dysfunction. However, DePinho *et al.* (13) produced clear evidence that azathioprine is an idiopathic hepatotoxin with the potential for inducing combined cholestatic and hepatocellular injury in man. Rats fed azathioprine-containing diets for 3 to 4 weeks develop severe liver damage, centrilobular necrosis and bile ductule proliferation, but not mononuclear cell infiltration; elevated  $\gamma$ -GTP and Al-Pase activities also are observed (14). While azathioprine may possibly account for the histological and biochemical changes observed in the present case, it is difficult to attribute all the clinicopathological features solely to this drug. Other hepatotoxic agents, such as methyldopum, may have been involved.

Cyclosporin A is a new immunosuppressive agent that improves allograft survival in renal transplant recipients without a concomitant increase in patient morbidity or mortality (15). However, recent reports (16, 17) suggest that dose-dependent and reversible hepatotoxicity is associated with rising serum bilirubin and Al-Pase in a number of renal-transplant recipients treated with cyclosporine. Further studies are needed to find a potent immunosuppressive agent for renal transplantation which is not hepatotoxic.

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